REMARKS

Claims 1-35 are pending in the present application. By virtue of this response, claims 1-35 have been cancelled. New claims 36-99 have been added. The specification is amended to correct typographical errors.

With respect to new claims:

- Independent claims 36 and 64 recite a polynucleotide comprising a region containing an Adeno-associated virus (AAV) inverted terminal repeat (ITR) and one or more heterologous transcriptionally active elements incorporated 3' with respect to the ITR, wherein at least one of the one or more heterologous transcriptionally active elements is a human transcriptionally active element. Dependent claims 37 to 51, 98, and 99 correspond to previously pending dependent claims 2-13, 18, 23, 24, 28, and 29 from claim 1.
- Independent claims 52 and 71 recite a polynucleotide comprising a region containing an Adeno-associated virus (AAV) inverted terminal repeat (ITR) and a heterologous segment incorporated 3' with respect to the ITR, wherein the heterologous segment comprises one or more transcriptionally active elements, wherein the heterologous segment is less than 500 nucleotides in length and is tissue specific, and wherein the heterologous segment has a deletion compared to its native sequence.
- Independent claims 58 and 80 recite a polynucleotide comprising a region containing an Adeno-associated virus (AAV) inverted terminal repeat (ITR) and a heterologous segment incorporated 3' with respect to the ITR, wherein the heterologous segment comprises one or more transcriptionally active elements which are removed from a promoter, and wherein the heterologous segment is less than 500 nucleotides in length and is tissue specific.

Support for the new claims 36-51, 64-70, 89-91, 98 and 99 is found in the previously pending claims, and in Examples 1-4 , 1-5, and 1-8. Support for the new claims 52-57, 71-79,

and 92-94 is found in the previously pending claims, and in the specification, *inter alia*, on page 24, lines 27-28, page 25, lines 2-3, and Examples 1-4, 1-5, and 1-9. Support for the new claims 58-63, 80-88, and 95-97 is found in the previously pending claims, and in the specification, *inter alia*, on page 24, lines 27-28, page 25, lines 2-3, and Examples 1-1, 1-3, 1-4, and 1-6 through 1-9. Claims 36-99 are currently under consideration.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made**".

With respect to all amendments and canceled claims, Applicant has not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicant reserves the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional application.

Double Patenting

Claims 1-35 are rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-35 of U.S. Patent No. 6,346,415.

Applicants will address this issue upon the Office's evaluation of the newly submitted claims.

Rejections under 35 USC § 112, second paragraph

Claims 1-35 are rejected as allegedly indefinite under 35 USC § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant respectfully notes that claims 1-35 have been canceled, and new claims 36-99 have been added. In the new claims, the phrase "transcriptionally-activitated ITR" has been deleted, and replaced with a phrase "a region containing an Adeno-associated virus (AAV)

inverted terminal repeat (ITR) and one or more heterologous transcriptionally active elements incorporated 3' with respect to the ITR" (claims 36 and 64), or "a region containing an Adeno-associated virus (AAV) inverted terminal repeat (ITR) and a heterologous segment incorporated 3' with respect to the ITR" (claims 52, 58, 71, and 80). New claims 36, 52, 58, 64, 71, and 80 recite that the ITR is an AAV ITR.

Applicant respectfully traverses the rejection under 35 U.S.C. § 112, second paragraph.

Claims 1-35 are rejected as allegedly indefinite for reciting "a transcriptionally-activated . . . inverted terminal repeat" because "the specification seems to define an 'activated ITR' as encompassing elements that are not actually included inside an ITR." Office Action, pages 2-3. The Examiner further asserts that it is unclear how the working examples can be considered "inverted terminal repeats" since the heterologous elements in the working examples are neither repeated nor inverted nor enclosed by elements that are inverted and/or repeated. Office Action, page 2.

Claims 1-35 have been cancelled, and the new claims do not use the phrase "transcriptionally-activated ITR." Instead, the new claims recite a phrase "a region containing an Adeno-associated virus (AAV) inverted terminal repeat (ITR) and one or more heterologous transcriptionally active elements incorporated 3' with respect to the ITR" (claims 36 and 64), or "a region containing an Adeno-associated virus (AAV) inverted terminal repeat (ITR) and a heterologous segment incorporated 3' with respect to the ITR" (claims 52, 58, 71, and 80). Because the phrase "transcriptionally-activated ITR" has been deleted from the claims and replaced with clarifying and preferred language, Applicant believes that the rejection is moot. Moreover the working examples are clearly encompassed within the claimed polynucleotide comprising a region containing an ITR and one or more heterologous transcriptionally activated elements or a heterologous segment comprising one or more transcriptionally activated elements incorporated 3' with respect to the ITR. Accordingly, Applicant believes that the new claims are clear, and respectfully requests that this rejection be withdrawn.

With respect to claims 1-35, the Examiner questions whether a "transcriptionally-activated inverted terminal repeat" differs from an unmodified ITR adjacent to "some small, active promoter." Office Action, page 2. Applicants will address this question when discussing the rejection of these claims under 35 USC 102(b) over Srivastava et al., below. To the extent that this question is meant to indicate a further basis for rejecting these claims as indefinite, Applicant submits that the language of the new claims should render this rejection moot, and that the rejection under section 112, paragraph 2 should be withdrawn.

The Examiner further questions whether a construct with AAV terminal 321-bp meets the limitations of claims 25 and 34. Office Action, page 3. Applicants will address this question when discussing the rejection of these claims under 35 USC 102(b) over Flotte et al. and Baudard et al., below. To the extent that this question is meant to indicate a further basis for rejecting these claims as indefinite, Applicant submits that the language of the new claims should render this rejection moot, and that the rejection under section 112, paragraph 2 should be withdrawn.

With respect to claims 25-27, the Examiner asks whether the term "ITR" is intended to refer to AAV ITR or whether there is "intent to claim ITRs from other types of viruses." Office Action, page 3. Applicant notes that the term "ITR" is defined in the specification as an inverted terminal repeat at either end of the AAV genome. *See* Specification, page 12, lines 11-12. Applicant believes that this definition clarifies that the term ITR refers to AAV ITR. For added clarification, however, claims 25-27 have been cancelled, and new claims 36, 52, 58, 64, 71, and 80 recite that the ITR is an AAV ITR.

Claims 1, 2, 25, 26, and 34 are rejected as allegedly indefinite under 35 USC § 112, second paragraph, for reciting either "about 200 bp" and "about 400 bp" because it is allegedly not clear from the specification what range of sizes are described. Claims 1, 2, 25, 26, and 34 have been cancelled. Applicant will address this rejection in the context of new claims 36, 37, 64, and 65. Applicant respectfully disagrees that use of the term "about" renders these claims indefinite.

The term "about" is accepted and widely used in patent practice and is clearly acceptable under the law. The word "about" does not have a universal meaning in patent claims; rather, its meaning depends on the technological facts of the particular case. Pall Corp. v. Micron Separations, Inc., 66 F.3d 1211, 1217-18 (Fed. Cir. 1995); *see also* U.S. Patent & Trademark Office, Manual of Patent Examining Procedure § 2173.05(b). "About" is neither broad nor arbitrary, but rather serves as a flexible term with a meaning similar to "approximately." Conopco, Inc. v. May Dep't Stores Co., 46 F.3d 1556, 1561 (Fed. Cir. 1994). Further, a search of the USPTO's web site reveals that the PTO has issued in excess of 22,000 patents between January 1996 and October 1, 2002 with the term "between about" included in the claim language. Indeed, the Office issued the parent to this case (U.S. 6,346,415) with claims containing the term "about" (see, e.g., claim 1). Applicant submits that the use of the word "about" in the present application is similarly acceptable under the law, and, in view of the disclosed subject matter, the specification, and the cited caselaw, it is entirely appropriate to describe this fragment length with the word "about." Accordingly, Applicant respectfully requests withdrawal of this rejection.

Rejections under 35 USC § 112 first paragraph

Claims 1-35 are rejected under 35 USC § 112, first paragraph, because the specification, while being enabling for constructs with a promoter 3' to the ITR, allegedly does not reasonably provide enablement for constructs with promoter elements internal to the ITR or 5' to the ITR.

Applicant disagrees with the rejection of claims 1-35 under section 112, first paragraph. The specification provides ample guidance on how to make and use the invention of transcriptionally activated ITRs. Pages 22-25, 27-30, 31-37, and 41 describe preparation of polynucleotides of the invention. Pages 37-39 describe how to test the transcriptional activity of AAV vectors containing transcriptionally-activated ITRs. Pages 39-41 teach how to produce viral particles from AAV vectors with transcriptionally-activated ITRs. Because Applicant has extensively taught how to make and use the invention in terms which correspond to the scope of

the claims, claims 1-35 are enabled and Applicant submits that this rejection should be withdrawn.

However, without acquiescing to the rejection, and in the interest of expediting prosecution, claims 1-35 have been cancelled, and new claims recite that the claimed polynucleotide comprises a region containing the ITR and one or more heterologous transcriptionally active elements or a heterologous segment incorporated 3' with respect to the ITR. As the Examiner indicated that such constructs are enabled by the specification, Applicant respectfully requests that this rejection be withdrawn.

Rejections under 35 USC § 102(b)

Claims 25-27, and 34 stand rejected as allegedly anticipated under 35 USC 102(b) by Flotte et al., *J. Biol. Chem.* 268:3781-3790 (1993) or Baudard et al., *Human Gene Therapy* 7:1309-1322 (1996). According to the Examiner, the pSA313 construct of Flotte et al. contains 263 bp of AAV terminal sequence containing 145 bp of ITR plus the adjacent AAV p5 promoter, and this construct is at least two-fold more transcriptionally active than the construct containing the 145-bp ITR alone. The Examiner asserts that Baudard et al. disclose an ITR-MDR1 construct containing 234 bp of AAV terminal sequence including the ITR and adjacent p5 promoter. Finally, the Examiner notes that claim 26 is included in the rejection because of the allegedly indefinite scope of "less than about 200 bp." Office Action, page 5.

Claims 25-27 and 34 have been cancelled, and new claims recite that the claimed polynucleotide comprises a region containing the ITR and one or more heterologous transcriptionally active elements or a heterologous segment. By contrast, Flotte et al. and Baudard et al. each disclose constructs comprising the 145 bp AAV ITR plus adjacent nucleotide sequences containing the AAV p5 promoter. Because these references do not disclose a transcriptionally-activated ITR comprising a heterologous transcriptionally activated element or a heterologous segment, Applicant believes that this amendment is sufficient to overcome the rejection. Prompt withdrawal of this rejection is respectfully requested.

Claims 1, 3, 8-10, 23, 24, 25, 27, 28, 30, and 34 stand rejected as allegedly anticipated under 35 USC § 102(b) by Srivastava, U.S. Patent Number 5,252,479. The Examiner cites Srivastava for the working example of a polynucleotide containing 191 bp of AAV ITR adjacent to a 224 bp fragment containing a parvovirus B19 p6 promoter (B19 residues 200-424). Office Action, page 5. The Examiner further states that the boundaries of Srivastava's "transcriptionally activated ITR" can be reasonably considered to be AAV nt -191 plus B19 nt 200-350 (a length of 341 nt) and thus the construct reasonably meets a limitation of "less than 400 bp" for the "transcriptionally activated ITR". The Examiner asserts that since the p6 promoter in B19 serves the same function as the p5 promoter in AAV, it is reasonable to assume an improvement comparable to the 2-10 fold improvement observed in ITR-p5 constructs (Flotte et al., and Wang et al.) even though Srivastava did not measure transcription activity relative to a wild-type AAV ITR. Office Action, page 6. The Examiner concluded that Srivastava construct necessarily and inherently meets the claimed limitations. Office Action, page 6.

In the interest of expediting prosecution and without acquiescing to the rejection, rejected claims 1, 3, 8-10, 23-25, 27, 28, 30, and 34 have been cancelled (claims 1-35 have been cancelled), and new claims recite that the claimed polynucleotide comprises a region containing an AAV ITR and one or more heterologous transcriptionally active elements wherein at least one of the one or more transcriptionally active elements is a human transcriptionally active element (claims 36 and 64), a region containing an AAV ITR and a heterologous segment comprising one or more transcriptionally active elements wherein the heterologous segment has a deletion compared to its native sequence (claims 52 and 71), or a region containing an AAV ITR and a heterologous segment comprising one or more transcriptionally active elements which are removed from a promoter (claims 58 and 80). By contrast, the construct of Srivastava et al. discloses the full B19p6 promoter, which is not a human promoter, does not have deletion compared to its native sequence, or is not removed from a promoter. *See* Srivastava et al., Col.

14, lines 16-19 and Fig. 2. Thus, Srivastava et al. do not disclose the claimed polynucleotides. Applicant respectfully requests that this rejection be withdrawn.

Claims 9 and 10 are further rejected as allegedly anticipated by Srivastava et al. on the ground that "both the B6 fragment and the APP promoter (in applicant's SEQ ID NO.7) contain a TATATA sequence and transcription initiation sequence about 30 nucleotides downstream," and thus the B6 promoter fragment allegedly contains a transcriptionally active element of an APP promoter and a transcription initiation sequence in a segment less than 70 nucleotides. Office Action, page 6.

Claims 9 and 10 have been cancelled; however, Applicant will address this rejection in the context of new claims 44 and 45, which correspond to cancelled claims 9 and 10. Applicant submits that because claims 44 and 45 depend from claim 36, the rejection must be withdrawn based on the arguments made above.[1]

Applicant respectfully requests that the rejection be withdrawn.

Rejections under 35 USC § 103(a)

Claims 25-27, and 34 stand rejected as allegedly being unpatentable under 35 USC § 103 over Carter et al., U.S. Patent Number 5,587,308. The Examiner cites Carter et al. as teaching "promoter activity in the AAV ITR in a fragment of 145 bp." Although the Examiner notes that this disclosure differs from the claimed invention, in that Carter et al. teach a wild-type ITR (not one with at least a two-fold increase in transcriptional activity), the Examiner asserts that Carter et al. teach several elements of the ITR which resemble known promoter elements and explicitly

[1] Applicant respectfully directs the Examiner's attention to Example 1-4 on page 33 of the specification, wherein it is clearly stated that the double-underlined sequences (nucleotides 33-66) are derived from the CMV promoter. The CMV promoter-derived sequences clearly include the TATA box and the transcriptional start site. Example 1-4 further states that "[t]he APP promoter is apparently devoid of . . . TATA boxes . . . ." Specification, page 33, line 10. Thus, it is evident that the TATA box is not a transcriptionally active element of an APP promoter. However, as stated above, because broader claims are not anticipated by Srivastava et al., newly submitted dependent claims 44 and 45 are likewise not anticipated.

suggest modification of the ITR to modulate the transcriptional activity through standard mutagenesis techniques. The Examiner states that it would be obvious to achieve at least a two-fold increase in transcriptional activity. Office Action, page 7.

As a preliminary matter, Carter does not suggest that transcriptional activity may be modulated such that at least a two-fold increase in transcription is achieved, as required by the claims. For this reason, Carter does not render claims 25-27 and 34 obvious. Moreover, without acquiescence to the rejection and in the interest of expediting prosecution, claims 25-27 and 34 have been cancelled, and new claims recite that the polynucleotide comprises a region containing an ITR and one or more heterologous transcriptionally active elements or a heterologous segment incorporated 3' with respect to the ITR. By contrast, as noted by the Examiner, Carter et al. identify two motifs within the ITR sequence that may be important in ITR promoter function, and suggest that standard mutagenesis techniques may be used "to alter the ITR sequence . . . to modulate the transcriptional activity of the ITR either up or down." Col. 14, lines 41-45; *see also,* lines 13-14. Thus, Carter neither teaches nor suggests a polynucleotide comprising a region containing an ITR and one or more heterologous transcriptionally active elements or a heterologous segment incorporated 3' with respect to the ITR. For the above-stated reasons, Applicant submits that Carter et al. do not render new claims obvious, and withdrawal of this rejection is respectfully requested.

Claims 31-33, and 35 stand rejected as allegedly unpatentable under 35 USC § 103 over Srivastava et al. as applied to claims 1, 3, 8-10, 23, 24, 25, 27, 28, 30 and 34 above, and further in view of Flotte et al., United States Patent No. 5,658,776 and Allen, WO 96/17947. The Examiner asserts that Flotte et al. teach the advantages of a packaging cell line with a stably integrated AAV vector, and Allen teaches the advantages of a packaging cell line with a stably integrated *rep* and *cap* genes. Accordingly, it would allegedly have been within the ordinary skill of the art to further modify the teachings of Srivastava et al. to produce a packaging cell line

with any or all of these integrated materials, to achieve the advantages taught by the secondary references. Office Action, pages 7-8.

Applicant respectfully notes that claims 31-33 and 35 have been cancelled; however, Applicant will address the rejection in the context of new claims 89-97, which correspond to claims 31-33.

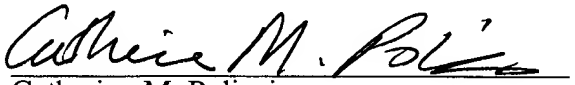
Applicant respectfully traverses this rejection. To establish a *prima facie* case of obviousness, three conditions must be met. First, there must be some suggestion, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP 2143, and 2143.01 to 2143.03); *In re Fine*, 837 F.2d 1071, 5 USPQ 2d 1596 (Fed. Cir. 1988). Applicant respectfully submits that the Examiner has not made a *prima facie* case of obviousness because each and every limitation is not taught or suggested in the prior art references even if combined. As noted above, Srivastava et al. do not disclose the claimed polynucleotide. Accordingly, Srivastava et al. alone, and further in view of Flotte et al., United States Patent No. 5,658,776 and Allen, WO 96/17947 do not teach or suggest each and every limitation of claims 89-97. Because a *prima facie* case of obviousness has not been made, Applicant requests withdrawal of this rejection.

CONCLUSION

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 226272003802.

Respectfully submitted,

Dated: March 3, 2003

By: 

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

Please substitute the paragraph starting on page 6 line 7 ending on page 6 line 16 with the following paragraph:

Several systems of using rAAV vectors to package foreign DNA and transduce it into various cells have been described. The first rAAV vectors that were described contained foreign reporter genes such as *neo, cat* or *dhfr* that were expressed from AAV transcription promoters or an SV40 promoter (Tratschin et al., 1984b, Mol. Cell. Biol. **4**:2072-2081; Hermonat and Muzyczka, 1984, Proc. Natl. Acad. Sci. USA, **81**:6466-6470; Tratschin et al., 1985, Mol. Cell. Biol. **5**:3251-3260; McLaughlin et al., 1988, J. Virol., **62**:1963-1973; Lebkowski et al., 1988 Mol. Cell. Biol., [**7**:349-356] **8**:3988-3996). These vectors were packaged into AAV-transducing particles by co-transfection into adenovirus-infected cells together with a second packaging plasmid that contained the AAV *rep* and *cap* genes expressed from the wild-type AAV transcription promoters.

Please substitute the paragraph starting on page 27 line 21 ending on page 28 line 7 with the following paragraph:

By way of illustration, a rAAV vector can comprise a transcriptionally-activated ITR operably linked to a polynucleotide that encodes a functional cystic fibrosis transmembrane conductance regulator polypeptide (CFTR) operably linked to a promoter. As is now known in the art, there are a variety of CFTR polypeptides that are capable of reconstructing CFTR functional deficiencies in cells derived from cystic fibrosis patients. As described in the commonly-owned U.S. Patent Application [08/445,552] 08/455,552 (which is proceeding to issuance), a truncated CFTR polypeptide, missing amino acids 1-118 of the wild-type protein, was able to restore a cAMP-regulated chloride ion conductance in cells with the cystic defect (IB3 cells). The portion of the CFTR cDNA that encodes amino acids 1-118 was deleted from

the full cDNA so that the polynucleotide could be packaged into a rAAV. Analogously, Rich et al. (1991, Science **253**: 205-207) described a CFTR derivative missing amino acid residues 708-835, that was capable of transporting chloride and capable of correcting a naturally occurring CFTR defect. To take two additional examples, Arispe et al. (1992, Proc. Natl. Acad. Sci. USA **89**: 1539-1543) showed that a CFTR fragment comprising residues 433-586 was sufficient to reconstitute a correct chloride channel in lipid bilayers; and Sheppard et al. (1994, Cell **76**: 1091-1098) showed that a CFTR polypeptide truncated at residue 836 to about half its length was still capable of building a regulated chloride channel. Thus, the native CFTR protein, and mutants and fragments thereof, all constitute CFTR polypeptides that are useful under this invention.

In the claims:

Please cancel claims 1-35 without prejudice or disclaimer.

Please add new claims 36-99.